RESPONSE UNDER 37 C.F.R. § 1.116
EXPEDITED PROCEDURE REQUESTED
EXAMINING GROUP 1615
PATENT
Customer No. 22,852
Attorney Docket No. 5273-34

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
Tadashi Mukai	Group Art Unit: 1615
Application No.: 10/089,442	Examiner: Humera N. Sheikh
Filed: March 29, 2002	Confirmation No.: 6933
For: Coated Preparation Soluble in the Lower Digestive Tract	**Mail Stop AF**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

REPLY

In the Office Action of June 21, 2005, the Examiner continued to reject claims 1-8 under 35 U.S.C. §103(a) for being obvious over Maruyama et al. in view of Eichel et al.

Applicants' invention, as set forth in claim 1, relates to a coating dispersion soluble in the lower digestive tract comprising a hydroxypropyl methylcellulose acetate succinate soluble at around pH 7, an acid, a plasticizer and an anion surfactant, wherein the hydroxypropyl methylcellulose acetate succinate has an average particle size of 10 μm or less which is dispersed at a concentration of from 2 to 20 % by weight in water, and the acid is present in an amount of from 1 to 10 parts by weight per 100 parts by weight of the hydroxypropyl methylcellulose acetate succinate.

The present invention also provides, as set forth in claim 7, a coated granule for delivery to the large intestine, which comprises a medicament-containing granular core that is coated with the coating dispersion soluble in the lower digestive tract.

The present invention thus provides a coated preparation for oral administration which can release medicament in the lower digestive tract, i.e., in the large intestine when administered orally, and a coating dispersion soluble in the lower digestive tract suitable for achieving such a purpose, the coating base material used therein being not immediately dissolved during passage through the ileum where pH values raise to about 7. It also provides a large intestine delivery coated granule preparation which can sufficiently release medicament in the large intestine and even after it has reached there.

Maruyama et al. discloses a dispersion of an enteric coating agent containing hydroxypropylmethyl cellulose acetate succinate (HPMCAS), a plasticizer and an anionic surfactant. However, as recognized by the Examiner, Maruyama et al. does not teach or even suggest the incorporation of an acid into the coating dispersion nor the effect thereof.

Eichel et al. discloses that an acid containing coating layer may optionally be applied onto or an acid may be included in an inner enteric coating layer of a sustained-release pharmaceutical preparation.

The Examiner therefore believes it would have been obvious to one of ordinary skill in the art to employ the acids of Eichel et al. in the coating dispersion of Maruyama et al.

In Eichel et al., it is essential to form a multi-walled coated drug, comprising an inner wall microencapsular enteric coating and an outer wall microencapsulated control coating, and it is the inner wall coating that contains the acid either layered onto it or included in it. In contrast, in applicants' invention, the acid is incorporated into the dispersion which forms the coating for the medicament. This then enables the coated preparation to deliver the medicament to the lower digestive tract, i.e., the large intestine and then release it in that region. There is no teaching in Eichel et al. that the acid on or in an inner layer would have this effect if included in the dispersion of Maruyama et al., because in Eichel et al. it is the outer wall microencapsular control coating that does not readily dissolve or disperse in either the stomach or the intestines and the acid is not in this layer.

Moreover, in the present invention it is essential that the acid be present in the coating dispersion in an amount of from 1 to 10 parts by weight per 100 parts by weight of the HPMCAS. As discussed at page 7, lines 5 to 13, when the acid is used in an amount less than 1 part by weight, the coating layer of the preparation will dissolve before reaching the lower digestive tract when administered, which results in insufficient release of the active ingredient in the large intestine. On the other hand, when the amount of the acid is too much and above the upper limit, the coating base material easily aggregates, which undesirably causes an unstable coating film.

In support of the critically of this claimed range of 1 to 10 parts by weight of acid per 100 parts by weight of the HPMCAS, enclosed is a declaration of Mr. T. Mukai, one of the inventors, that sets forth a comparative experiment he carried out to show that when none and when the larger amounts of acid are used as disclosed in Eichel et al,

the desired effects of sufficient release of the active ingredient in the large intestine will not be obtained.

With reference to the declaration and the comparative experiment shown, when a larger amount of an acid was used in the coating dispersion (e.g., 50 parts by weight of citric acid to 100 parts by HPMCAS), the active ingredient showed much less time lag in the dissolution rate compared with the present invention where the citric acid was used in an amount of 3 parts by weight to 100 parts by weight of HPMCAS, which is within the claimed range of 1 to 10 parts by weight per 100 parts by weight of the HPMCAS. Thus according to these comparative experimental results, when an acid is used in a larger amount in the coating dispersion as disclosed in Eichel et al., the coating layer of the preparation will dissolve before reaching the lower digestive tract. Hence the active ingredient contained in the preparation will be dissolved out before reaching the large intestine which results in insufficient release of the active ingredient in the large intestine. On the other hand, according to the present invention, when the acid in the coating dispersion is used in an amount of from 1 to 10 parts by weight to 100 parts by weight of HPMCAS, the dissolving rate has sufficient time lag so that it can release the active ingredient in a sufficient amount in the large intestine. Note that the lag time is approximately five times longer. Compare the dissolution time of the product of the invention with the dissolution times of the products of Comp. Ex. B. It even was nearly five times longer when compared with the dissolution time of the product of Comp. Ex. A which contained no citric acid.

This Experiment clearly establishes the criticality of the claimed range in view of the superior effects obtained. Accordingly, it is submitted that this is sufficient to

demonstrate the unexpected and/or unusual results attributed by the claimed acid content the Examiner required to overcome the prima facie case of obviousness based on the cited references since the prior art does not teach applicants' claimed amounts of acid. See page 7, second paragraph of the Office Action.

Withdrawal of the rejection of claims 1-8 over the cited combination of references and their allowance is therefore requested.

A RCE is being filed with this Reply to enable the Examiner to consider the Declaration at this time.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: December 21, 2005

By: _____
Arthur S. Garrett
Reg. No. 20,338

Attachment: Declaration of inventor Tadashi Mukai

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